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(71) Applicant (*for all designated States except US*): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): GIBSON, Keith, Hopkinson [GB/GB]; Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: TAIT, Brian, Steele; ZENECA Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

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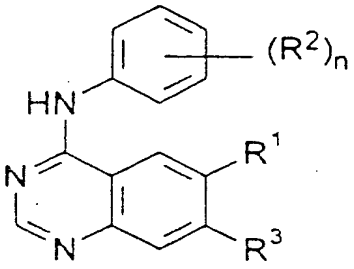
(54) Title: QUINAZOLINE DERIVATIVES

(57) Abstract

The invention concerns quinazoline derivatives of the formula (I) wherein n is 1, 2 or 3 and each R^2 is independently halogeno, trifluoromethyl or (1-4C)alkyl; R^3 is (1-4C)alkoxy; and R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy, di-[(1-4C)alkoxy-(2-4C)alkoxyl]amino-(2-4C)alkoxy, thiamorpholino-(2-4C)alkoxy, 1-oxothiamorpholino-(2-4C)alkoxy or 1,1-dioxothiamorpholino-(2-4C)alkoxy, and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent; or pharmaceutically-acceptable salts thereof; processes for their preparation, pharmaceutical compositions containing them, and the use of the receptor tyrosine kinase inhibitory properties of the compounds in the treatment of proliferative disease such as cancer.



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QUINAZOLINE DERIVATIVES

The invention relates to quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-proliferative activity such as anti-cancer activity and are accordingly useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said quinazoline derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to anti-proliferative agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene i.e. a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. The growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden et al., Ann. Rev. Biochem., 1988, 57, 443; Larsen et al. Ann. Reports in Med. Chem. 1989, Chpt. 13).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60, 43-73) based on families of growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, NEU, erbB, Xmrk, HER and let23

receptors. Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin, IGFI and insulin-related receptor (IRR) receptors and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors. It is known that Class I kinases such as the EGF family of receptor tyrosine kinases are frequently present in common human cancers such as breast cancer (Sainsbury et al., Brit. J. Cancer, 1988, 58, 458; Guerin et al., Oncogene Res., 1988, 3, 21 and Klijn et al., Breast Cancer Res. Treat., 1994, 29, 73), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny et al., Brit. J. Cancer, 1986, 54, 265; Reubi et al., Int. J. Cancer, 1990, 45, 269; and Rusch et al., Cancer Research, 1993, 53, 2379) and squamous cell cancer of the lung (Hendler et al., Cancer Cells, 1989, 7, 347), bladder cancer (Neal et al., Lancet, 1985, 366), oesophageal cancer (Mukaida et al., Cancer, 1991, 68, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen et al., Oncogene Res., 1987, 1, 149), cancer of the prostate (Visakorpi et al., Histochem. J., 1992, 24, 481), leukaemia (Konaka et al., Cell, 1984, 37, 1035) and ovarian, bronchial or pancreatic cancer (European Patent Specification No. 0400586). As further human tumour tissues are tested for the EGF family of receptor tyrosine kinases it is expected that their widespread prevalance will be established in further cancers such as thyroid and uterine cancer. It is also known that EGF type tyrosine kinase activity is rarely detected in normal cells whereas it is more frequently detectable in malignant cells (Hunter, Cell, 1987, 50, 823). It has been shown more recently (W J Gullick, Brit. Med. Bull., 1991, 47, 87) that EGF receptors which possess tyrosine kinase activity are overexpressed in many human cancers such as brain, lung squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynaecological and thyroid tumours.

Accordingly it has been recognised that an inhibitor of receptor tyrosine kinases should be of value as a selective inhibitor of the growth of mammalian cancer cells (Yaish et al. Science, 1988, 242, 933). Support for this view is provided by the demonstration that erbstatin, an EGF receptor tyrosine kinase inhibitor, specifically attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma which expresses EGF receptor tyrosine kinase but is without effect on the growth of another carcinoma which does not express EGF receptor tyrosine kinase (Toi et al., Eur. J. Cancer Clin. Oncol., 1990, 26, 722.) Various derivatives of styrene are also stated to possess tyrosine kinase inhibitory

properties (European Patent Application Nos. 0211363, 0304493 and 0322738) and to be of use as anti-tumour agents. The in vivo inhibitory effect of two such styrene derivatives which are EGF receptor tyrosine kinase inhibitors has been demonstrated against the growth of human squamous cell carcinoma inoculated into nude mice (Yoneda et al., Cancer Research, 1991, 51, 4430). Various known tyrosine kinase inhibitors are disclosed in a more recent review by T R Burke Jr. (Drugs of the Future, 1992, 17, 119).

It is known from European Patent Applications Nos. 0520722, 0566226 and 0635498 that certain quinazoline derivatives which bear an anilino substituent at the 4-position possess receptor tyrosine kinase inhibitory activity. It is further known from European Patent Application No. 0602851 that certain quinazoline derivatives which bear a heteroarylamino substituent at the 4-position also possess receptor tyrosine kinase inhibitory activity.

It is further known from International Patent Application WO 92/20642 that certain aryl and heteroaryl compounds inhibit EGF and/or PDGF receptor tyrosine kinase. There is the disclosure of certain quinazoline derivatives therein but no mention is made of 4-anilinoquinazoline derivatives.

The in vitro anti-proliferative effect of a 4-anilinoquinazoline derivative has been disclosed by Fry et al., Science, 1994, 265, 1093. It was stated that the compound 4-(3'-bromoanilino)-6,7-dimethoxyquinazoline was a highly potent inhibitor of EGF receptor tyrosine kinase.

The in vivo inhibitory effect of a 4,5-dianilinophthalimide derivative which is an inhibitor of the EGF family of receptor tyrosine kinases has been demonstrated against the growth in BALB/c nude mice of a human epidermoid carcinoma A-431 or of a human ovarian carcinoma SKOV-3 (Buchdunger et al., Proc. Nat. Acad. Sci., 1994, 91, 2334).

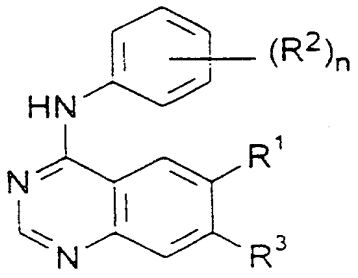
It is further known from European Patent Application No. 0635507 that certain tricyclic compounds which comprise a 5- or 6-membered ring fused to the benzo-ring of a quinazoline possess receptor tyrosine kinase inhibitory activity. It is also known from European Patent Application No. 0635498 that certain quinazoline derivatives which carry an amino group at the 6-position and a halogeno group at the 7-position possess receptor tyrosine kinase inhibitory activity.

Accordingly it has been indicated that Class I receptor tyrosine kinase inhibitors will prove to be useful in the treatment of a variety of human cancers

EGF type receptor tyrosine kinases have also been implicated in non-malignant proliferative disorders such as psoriasis (Elder et al., Science, 1989, 243, 811). It is therefore expected that inhibitors of EGF type receptor tyrosine kinases will be useful in the treatment of non-malignant diseases of excessive cellular proliferation such as psoriasis (where TGFα is believed to be the most important growth factor), benign prostatic hypertrophy (BPH), atherosclerosis and restenosis.

There is no disclosure in these documents of quinazoline derivatives which bear at the 4-position an anilino substituent and which also bear an alkoxy substituent at the 7-position and a dialkylaminoalkoxy substituent at the 6-position. We have now found that such compounds possess potent in vivo anti-proliferative properties which are believed to arise from their Class I receptor tyrosine kinase inhibitory activity.

According to the present invention there is provided a quinazoline derivative of the formula I



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wherein n is 1, 2 or 3 and each R^2 is independently halogeno, trifluoromethyl or (1-4C)alkyl; R^3 is (1-4C)alkoxy; and

R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy, di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(2-4C)alkoxy, thiamorpholino-(2-4C)alkoxy, 1-oxothiamorpholino-(2-4C)alkoxy or 1,1-dioxothiamorpholino-(2-4C)alkoxy, and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent;

or a pharmaceutically-acceptable salt thereof.

According to a further aspect of the present invention there is provided a quinazoline derivative of the formula I

wherein n is 1, 2 or 3 and each R^2 is independently halogeno, trifluoromethyl or (1-4C)alkyl;

R^3 is (1-4C)alkoxy; and

R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy or di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(2-4C)alkoxy,

and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent;

or a pharmaceutically-acceptable salt thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example when R^1 is a di-[(1-4C)alkyl]amino-(2-4C)alkoxy group, suitable values for this generic radical include 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 2-dimethylaminopropoxy and 1-dimethylaminoprop-2-yloxy. An analogous convention applies to other generic terms.

Within the present invention it is to be understood that, insofar as certain of the compounds of the formula I may exist in optically active or racemic forms by virtue of one or more substituents containing an asymmetric carbon atom, the invention encompasses any such optically active or racemic form which possesses anti-proliferative activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

The quinazolines of the formula I are unsubstituted at the 2-, 5- and 8-positions.

It is also to be understood that certain quinazoline derivatives of the formula I can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess anti-proliferative activity.

Suitable values for the generic radicals referred to above include those set out below.

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A suitable value for R^2 when it is halogeno is, for example fluoro, chloro, bromo or iodo; and when it is (1-4C)alkyl is, for example, methyl, ethyl, propyl, isopropyl or butyl.

A suitable value for R^3 when it is (1-4C)alkoxy is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy.

Suitable values for each R^1 substituent which may be present on the quinazoline ring include, for example:-

for di-[(1-4C)alkyl]amino-(2-4C)alkoxy: 2-dimethylaminoethoxy, 2-(N-ethyl-N-methylamino)ethoxy, 2-diethylaminoethoxy, 2-dipropylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-dimethylaminopropoxy, 2-diethylaminopropoxy, 1-dimethylaminoprop-2-yloxy, 1-diethylaminoprop-2-yloxy, 1-dimethylamino-2-methylprop-2-yloxy, 2-dimethylamino-2-methylpropoxy, 4-dimethylaminobutoxy, 4-diethylaminobutoxy, 3-dimethylaminobutoxy, 3-diethylaminobutoxy, 2-dimethylaminobutoxy, 2-diethylaminobutoxy, 1-dimethylaminobut-2-yloxy and 1-diethylaminobut-2-yloxy;

for pyrrolidin-1-yl-(2-4C)-alkoxy: 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy and 4-(pyrrolidin-1-yl)butoxy;

for piperidino-(2-4C)alkoxy: 2-piperidinoethoxy, 3-piperidinopropoxy and 4-piperidinobutoxy;

for morpholino-(2-4C)alkoxy: 2-morpholinoethoxy, 3-morpholinopropoxy and 4-morpholinobutoxy;

for piperazin-1-yl-(2-4C)alkoxy: 2-(piperazin-1-yl)ethoxy, 3-(piperazin-1-yl)propoxy and 4-(piperazin-1-yl)butoxy.

for 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy:	2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy and 4-(4-methylpiperazin-1-yl)butoxy;
for imidazol-1-yl-(2-4C)alkoxy:	2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy and 4-(imidazol-1-yl)butoxy;
for di-[(1-4C)alkoxy-(2-4C)-alkyl]amino-(2-4C)alkoxy:	2-[di-(2-methoxyethyl)amino]ethoxy, 3-[di-(2-methoxyethyl)amino]propoxy, 2-[di-(3-methoxypropyl)amino]ethoxy and 3-[di-(3-methoxypropyl)amino]propoxy;
for thiamorpholino-(2-4C)alkoxy:	2-thiamorpholinoethoxy, 3-thiamorpholinopropoxy and 4-thiamorpholinobutoxy;
for 1-oxothiamorpholino-(2-4C)alkoxy:	2-(1-oxothiamorpholino)ethoxy, 3-(1-oxothiamorpholino)propoxy and 4-(1-oxothiamorpholino)butoxy;
for 1,1-dioxothiamorpholino-(2-4C)alkoxy:	2-(1,1-dioxothiamorpholino)ethoxy, 3-(1,1-dioxothiamorpholino)propoxy and 4-(1,1-dioxothiamorpholino)butoxy.

Suitable substituents formed when any of the R^1 substituents comprising a CH_2 group which is not attached to a N or O atom bears on said CH_2 group a hydroxy substituent include, for example, substituted di-[(1-4C)alkyl]amino-(2-4C)alkoxy groups, for example hydroxy-di-[(1-4C)alkyl]amino-(2-4C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy.

A suitable pharmaceutically-acceptable salt of a quinazoline derivative of the invention is, for example, an acid-addition salt of a quinazoline derivative of the invention which is sufficiently basic, for example, a mono- or di-acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, maleic, tartaric, fumaric, methanesulphonic or 4-toluenesulphonic acid

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Particular novel compounds of the invention include, for example, quinazoline derivatives of the formula I, or pharmaceutically-acceptable salts thereof, wherein:-

(a) n is 1 or 2 and each R^2 is independently fluoro, chloro, bromo, trifluoromethyl or methyl; and R^3 and R^1 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(b) n is 1, 2 or 3 and each R^2 is independently fluoro, chloro or bromo; and R^3 and R^1 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(c) R^3 is methoxy or ethoxy; and n, R^2 and R^1 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(d) R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(piperazin-1-yl)ethoxy, 3-(piperazin-1-yl)propoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, 2-[di-(2-methoxyethyl)amino]ethoxy, 3-[di-(2-methoxyethyl)amino]propoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylamino-2-hydroxypropoxy, 3-(pyrrolidin-1-yl)-2-hydroxypropoxy, 3-piperidino-2-hydroxypropoxy, 3-morpholino-2-hydroxypropoxy, 3-(piperazin-1-yl)-2-hydroxypropoxy or 3-(4-methylpiperazin-1-yl)-2-hydroxypropoxy;
and n, R^2 and R^3 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(e) R^1 is 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(pyrrolidin-1-yl)propoxy, 3-piperidinopropoxy, 3-morpholinopropoxy, 3-(piperazin-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(imidazol-1-yl)propoxy, 3-[di-(2-methoxyethyl)amino]propoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylamino-2-hydroxypropoxy, 3-(pyrrolidin-1-yl)-2-hydroxypropoxy, 3-piperidino-2-hydroxypropoxy, 3-morpholino-2-hydroxypropoxy, 3-(piperazin-1-yl)-2-hydroxypropoxy or 3-(4-methylpiperazin-1-yl)-2-hydroxypropoxy;
and n, R^2 and R^3 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention.

(f) R^1 is 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(pyrrolidin-1-yl)propoxy, 3-morpholinopropoxy or 3-morpholino-2-hydroxypropoxy; and n, R^2 and R^3 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(g) R^1 is 3-morpholinopropoxy; and n, R^2 and R^3 have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention.

A preferred compound of the invention is a quinazoline derivative of the formula I wherein $(R^2)_n$ is 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
R^3 is methoxy; and
R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, 2-[di-(2-methoxyethyl)amino]ethoxy or 3-morpholino-2-hydroxypropoxy;
or a pharmaceutically-acceptable mono- or di-acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I
wherein $(R^2)_n$ is 3'-chloro, 3'-bromo, 3'-methyl, 2',4'-difluoro, 2',4'-dichloro, 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
R^3 is methoxy; and
R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(imidazol-1-yl)ethoxy, 2-[di-(2-methoxyethyl)amino]ethoxy or 3-morpholino-2-hydroxypropoxy;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I
wherein $(R^2)_n$ is 3'-chloro, 3'-bromo, 3'-methyl, 2',4'-difluoro, 2',4'-dichloro, 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;
R^3 is methoxy; and

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R^1 is 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(pyrrolidin-1-yl)propoxy, 3-morpholinopropoxy or 3-morpholino-2-hydroxypropoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further preferred compound of the invention is a quinazoline derivative of the formula I

wherein $(R^2)_n$ is 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;

R^3 is methoxy; and

R^1 is 3-morpholinopropoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

A specific preferred compound of the invention is the following quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-pyrrolidin-1-ylethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-morpholinoethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-{2-[di-(2-methoxyethyl)amino]ethoxy}-quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-6-(2-dimethylaminoethoxy)-7-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-6-(2-diethylaminoethoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(2',4'-difluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-6-(2-hydroxy-3-morpholinopropoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(2',4'-difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-6-(2-imidazol-1-ylethoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-6-(3-diethylaminopropoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-pyrrolidin-1-ylpropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I -

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4-(3',4'-difluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3',4'-difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
6-(3-diethylaminopropoxy)-4-(3',4'-difluoroanilino)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-piperidinopropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-piperidinoethoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

A further specific preferred compound of the invention is the following quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-6-(3-imidazol-1-ylpropoxy)-7-methoxyquinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

In a further aspect of the invention it has been found that certain of the compounds of the invention possess not only the property of potent in vivo anti-proliferative activity whereby the rate of growth of tumour tissue is slowed but also the property of being able to arrest the growth of tumour tissue and, at higher doses, of being able to cause shrinkage of the original tumour volume.

According to this aspect of the invention there is provided the quinazoline derivative of the formula I:-
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline;
or a pharmaceutically-acceptable acid-addition salt thereof.

There is also provided the hydrochloride salt of the quinazoline derivative of the formula I:-

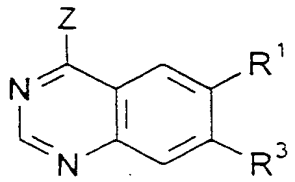
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline.

There is also provided the dihydrochloride salt of the quinazoline derivative of the formula I:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline.

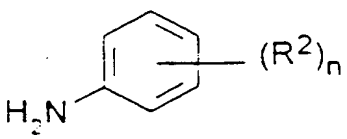
A quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes include, for example, those illustrated in European Patent Applications Nos. 0520722, 0566226, 0602851, 0635498 and 0635507. Such processes, when used to prepare a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated, n, R^2, R^3 and R^1 have any of the meanings defined hereinbefore for a quinazoline derivative of the formula I. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described within the accompanying non-limiting Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) The reaction, conveniently in the presence of a suitable base, of a quinazoline of the formula II



II

wherein Z is a displaceable group, with an aniline of the formula III



III

A suitable displaceable group Z is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively a suitable base is, for example, an alkali metal or alkaline earth metal amide, for example sodium amide or sodium bis(trimethylsilyl)amide.

The reaction is preferably carried out in the presence of a suitable inert solvent or diluent, for example an alkanol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

The quinazoline derivative of the formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-Z wherein Z has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base as defined hereinbefore using a conventional procedure.

(b) For the production of those compounds of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the formula I wherein R^1 is a hydroxy group.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to amino-substituted alkoxy, for example an amino-substituted alkyl halide, for example an amino-substituted (2-4C)alkyl chloride, bromide or iodide, in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near 80°C.

(c) For the production of those compounds of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a compound of the formula I wherein R^1 is a hydroxy-(2-4C)alkoxy group, or a reactive derivative thereof, with an appropriate amine.

A suitable reactive derivative of a compound of the formula I wherein R^1 is a hydroxy-(2-4C)alkoxy group is, for example, a halogeno- or sulphonyloxy-(2-4C)alkoxy group such as a bromo- or methanesulphonyloxy-(2-4C)alkoxy group.

The reaction is preferably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, conveniently at or near 50°C.

(d) For the production of those compounds of the formula I wherein R^1 is a hydroxy-amino-(2-4C)alkoxy group, the reaction of a compound of the formula I wherein R^1 is a 2,3-epoxypropoxy or 3,4-epoxybutoxy group with an appropriate amine.

The reaction is preferably carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 150°C, conveniently at or near 70°C.

When a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required, for example a mono- or di-acid-addition salt of a quinazoline derivative of the formula I, it may be obtained, for example, by reaction of said compound with, for example, a suitable acid using a conventional procedure.

As stated hereinbefore the quinazoline derivatives defined in the present invention possess anti-proliferative activity which is believed to arise from the Class I receptor tyrosine kinase inhibitory activity of the compounds. These properties may be assessed, for example, using one or more of the procedures set out below:-

(a) An in vitro assay which determines the ability of a test compound to inhibit the enzyme EGF receptor tyrosine kinase. Receptor tyrosine kinase was obtained in partially purified form from A-431 cells (derived from human vulval carcinoma) by the procedures described below which are related to those described by Carpenter et al., J. Biol. Chem., 1979, 254, 4884, Cohen et al., J. Biol. Chem., 1982, 257, 1523 and by Braun et al., J. Biol. Chem., 1984, 259, 2051.

A-431 cells were grown to confluence using Dulbecco's modified Eagle's medium (DMEM) containing 5% fetal calf serum (FCS). The obtained cells were homogenised in a

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hypotonic borate/EDTA buffer at pH 10.1. The homogenate was centrifuged at 400 g for 10 minutes at 0-4°C. The supernatant was centrifuged at 25,000 g for 30 minutes at 0-4°C. The pelleted material was suspended in 30 mM Hepes buffer at pH 7.4 containing 5% glycerol, 4 mM benzamidine and 1% Triton X-100, stirred for 1 hour at 0-4°C, and recentrifuged at 100,000 g for 1 hour at 0-4°C. The supernatant, containing solubilised receptor tyrosine kinase, was stored in liquid nitrogen.

For test purposes 40 µl of the enzyme solution so obtained was added to a mixture of 400 µl of a mixture of 150 mM Hepes buffer at pH 7.4, 500 µM sodium orthovanadate, 0.1% Triton X-100, 10% glycerol, 200 µl water, 80 µl of 25 mM DTT and 80µl of a mixture of 12.5 mM manganese chloride, 125 mM magnesium chloride and distilled water. There was thus obtained the test enzyme solution.

Each test compound was dissolved in dimethylsulphoxide (DMSO) to give a 50 mM solution which was diluted with 40 mM Hepes buffer containing 0.1% Triton X-100, 10% glycerol and 10% DMSO to give a 500 µM solution. Equal volumes of this solution and a solution of epidermal growth factor (EGF; 20 µg/ml) were mixed.

[γ-^{32}P]ATP (3000 Ci/mM, 250 µCi) was diluted to a volume of 2 ml by the addition of a solution of ATP (100 µM) in distilled water. An equal volume of a 4 mg/ml solution of the peptide Arg-Arg-Leu-Ile-Glu-Asp-Ala-Glu-Tyr-Ala-Ala-Arg-Gly in a mixture of 40 mM Hepes buffer at pH 7.4, 0.1% Triton X-100 and 10% glycerol was added.

The test compound/EGF mixture solution (5 µl) was added to the test enzyme solution (10 µl) and the mixture was incubated at 0-4°C for 30 minutes. The ATP/peptide mixture (10 µl) was added and the mixture was incubated at 25°C for 10 minutes. The phosphorylation reaction was terminated by the addition of 5% trichloroacetic acid (40 µl) and bovine serum albumin (BSA; 1 mg/ml, 5 µl). The mixture was allowed to stand at 4°C for 30 minutes and then centrifuged. An aliquot (40 µl) of the supernatant was placed onto a strip of Whatman p 81 phosphocellulose paper. The strip was washed in 75 mM phosphoric acid (4 x 10 ml) and blotted dry. Radioactivity present in the filter paper was measured using a liquid scintillation counter (Sequence A). The reaction sequence was repeated in the absence of the EGF (Sequence B) and again in the absence of the test compound (Sequence C)

Receptor tyrosine kinase inhibition was calculated as follows -

$$\% \text{ Inhibition} = \frac{100 - (A-B)}{C - B} \times 100$$

The extent of inhibition was then determined at a range of concentrations of test compound to give an IC_{50} value.

(b) An in vitro assay which determines the ability of a test compound to inhibit the EGF-stimulated growth of the human naso-pharyngeal cancer cell line KB.

KB cells were seeded into wells at a density of 1×10^4 - 1.5×10^4 cells per well and grown for 24 hours in DMEM supplemented with 5% FCS (charcoal-stripped). Cell growth was determined after incubation for 3 days by the extent of metabolism of MTT tetrazolium dye to furnish a bluish colour. Cell growth was then determined in the presence of EGF (10 ng/ml) or in the presence of EGF (10 ng/ml) and a test compound at a range of concentrations. An IC_{50} value could then be calculated.

(c) An in-vivo assay in a group of athymic nude mice (strain ONU:Alpk) which determines the ability of a test compound (usually administered orally as a ball-milled suspension in 0.5% polysorbate) to inhibit the growth of xenografts of the human vulval epidermoid carcinoma cell line A-431.

A-431 cells were maintained in culture in DMEM supplemented with 5% FCS and 2mM glutamine. Freshly cultured cells were harvested by trypsinization and injected subcutaneously (10 million cells/0.1 ml/mouse) into both flanks of a number of donor nude mice. When sufficient tumour material was available (after approximately 9 to 14 days), fragments of tumour tissue were transplanted in the flanks of recipient nude mice (test day 0). Generally, on the seventh day after transplantation (test day 7) groups of 7 to 10 mice with similar-sized tumours were selected and dosing of the test compound was commenced. Once daily dosing of test compound was continued for a total of 13 days (test days 7 to 19 inclusive). In some studies the dosing of the test compound was continued beyond test day 19, for example to test day 26. In each case, on the following test day the animals were killed and the final tumour volume was calculated from measurements of the length and width of the tumours. Results were calculated as a percentage inhibition of tumour volume relative to untreated controls.

Although the pharmacological properties of the compounds of the formula I vary with structural change as expected, in general activity possessed by compounds of the formula

l may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b) and (c):-

Test (a):- IC_{50} in the range, for example, 0.01-1 μM;

Test (b):- IC_{50} in the range, for example, 0.05-1 μM;

Test (c):- 20 to 90% inhibition of tumour volume from a daily dose in the range, for example, 12.5 to 200 mg/kg.

Thus, by way of example, the compounds described in the accompanying Examples possess activity at approximately the following concentrations or doses in tests (a) and (b).

Example	Test (a) IC_{50} (μM)	Test (b) IC_{50} (μM)
1	0.02	0.1
2	0.09	0.7
3	0.01	0.4
4	0.01	0.1
5	0.06	0.2
6	0.01	0.1
7	0.09	0.3
8	0.48	0.9
9	0.01	0.1
12	0.06	0.16
13	0.07	0.12
14	0.67	0.3
15	0.07	0.64
17	0.05	0.15
18	0.27	0.39
19	0.52	0.45
20	0.67	0.55

Example	Test (a) IC_{50} (μM)	Test (b) IC_{50} (μM)
21	0.08	0.12
22	0.1	0.19
23	0.08	0.16

In addition all of the compounds described in the accompanying Examples possess activity in test (c) with ED_{50} values of less than or equal to 200 mg/kg/day. In particular, the compound described in Example 1 hereinafter possesses activity in test (c) with an ED_{50} value of approximately 12.5 mg/kg.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intraveous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The quinazoline derivative will normally be administered to a warm-blooded animal at a unit dose within the range 5-10000 mg per square meter body area of the animal, i.e. approximately 0.1-200 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-100 mg/kg is employed. For the quinazoline derivative of Example 1, or a pharmaceutically-acceptable salt thereof, a daily dose of approximately 1 to 20 mg/kg, preferably of 1 to 5 mg kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a quinazoline derivative of the formula I as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties which are believed to arise from their Class I receptor tyrosine kinase inhibitory activity. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by Class I receptor tyrosine kinases, i.e. the compounds may be used to produce a Class I receptor tyrosine kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of Class I receptor tyrosine kinases, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of Class I receptor tyrosine kinase. Accordingly the compounds of the present invention are expected to be useful in the treatment of psoriasis and/or cancer by providing an anti-proliferative effect, particularly in the treatment of Class I receptor tyrosine kinase sensitive cancers such as cancers of the breast, lung, colon, rectum, stomach, prostate, bladder, pancreas and ovary.

Thus according to this aspect of the invention there is provided the use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative as defined immediately above.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular proliferative disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-200 mg/kg, preferably 1-100 mg/kg, more preferably 1-10 mg/kg is envisaged.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the quinazoline derivative of the invention, one or more

other anti-tumour substances, for example cytotoxic or cytostatic anti-tumour substances, for example those selected from, for example, mitotic inhibitors, for example vinblastine, vindesine and vinorelbine; tubulin disassembly inhibitors such as taxol; alkylating agents, for example cis-platin, carboplatin and cyclophosphamide; antimetabolites, for example 5-fluorouracil, tegafur, methotrexate, cytosine arabinoside and hydroxyurea, or, for example, one of the preferred antimetabolites disclosed in European Patent Application No. 239362 such as N-{5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-methylamino]-2-thenoyl}-L-glutamic acid; intercalating antibiotics, for example adriamycin, mitomycin and bleomycin; enzymes, for example asparaginase; topoisomerase inhibitors, for example etoposide and camptothecin; biological response modifiers, for example interferon; anti-hormones, for example antioestrogens such as tamoxifen, for example antiandrogens such as 4'-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)-propionanilide or, for example LHRH antagonists or LHRH agonists such as goserelin, leuprorelin or buserelin and hormone synthesis inhibitors, for example aromatase inhibitors such as those disclosed in European Patent Application No. 0296749, for example 2,2'-[5-(1H-1,2,4- triazol-1-ylmethyl)-1,3-phenylene]bis(2-methylpropionitrile), and, for example, inhibitors of 5α-reductase such as 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-en-3-one. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

As stated above the quinazoline derivative defined in the present invention is an effective anti-cancer agent, which property is believed to arise from its Class I receptor tyrosine kinase inhibitory properties. Such a quinazoline derivative of the invention is expected to possess a wide range of anti-cancer properties as Class I receptor tyrosine kinases have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a quinazoline derivative of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a quinazoline derivative of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas

It is further expected that a quinazoline derivative of the invention will possess activity against other diseases involving excessive cellular proliferation such as psoriasis and benign prostatic hypertrophy (BPH).

It is also to be expected that a quinazoline derivative of the invention will be useful in the treatment of additional disorders of cellular growth in which aberrant cell signalling by way of receptor tyrosine kinase enzymes or non-receptor tyrosine kinase enzymes, including as yet unidentified tyrosine kinase enzymes, are involved. Such disorders include, for example, inflammation, angiogenesis, vascular restenosis, immunological disorders, pancreatitis, kidney disease and blastocyte maturation and implantation.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids such as drying agents by filtration, unless otherwise stated magnesium sulphate was used as a drying agent for organic solutions;

(ii) operations were carried out at ambient temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) melting points were determined using a Mettler SP62 automatic melting point apparatus, an oil-bath apparatus or a Koffler hot plate apparatus.

(vi) the structures of the end-products of the formula I were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet, unless otherwise stated end-products of the formula I were dissolved in CD_3SOCD_3 for the determination of NMR values;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), infra-red (IR) or NMR analysis;

(viii) the following abbreviations have been used:-

DMF	N,N-dimethylformamide;
DMSO	dimethylsulphoxide;
THF	tetrahydrofuran;
DMA	N,N-dimethylacetamide.

Example 1

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1 g), 3-morpholinopropyl chloride (J. Amer. Chem.Soc., 1945, 67, 736; 0.62 g), potassium carbonate (2.5 g) and DMF (50 ml) was stirred and heated to 80°C for 2 hours. A further portion (0.1 g) of 3-morpholinopropyl chloride was added and the mixture was heated to 80°C for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using a 4:1 mixture of ethyl acetate and methanol as eluent. The material so obtained was recrystallised from toluene. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (0.69 g, 50%), m.p. 119-120°C;
NMR Spectrum: 2.0 (m, 2H), 2.45 (m, 6H), 3.6 (m, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 58.7; H, 5.3; N, 12.2;
$C_{22}H_{24}ClFN_4O_3$ requires C, 59.1; H, 5.4; N, 12.5%.

The 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline used as a starting material was obtained as follows:-

6,7-Dimethoxy-3,4-dihydroquinazolin-4-one (European Patent Application No. 0 566 226, Example 1 thereof; 26.5 g) was added portionwise to stirred methanesulphonic acid (175 ml). L-Methionine (22 g) was added and the resultant mixture was stirred and heated to reflux for 5 hours. The mixture was cooled to ambient temperature and poured onto a mixture (750 ml) of ice and water. The mixture was neutralised by the addition of a concentrated (40%) aqueous sodium hydroxide solution. The precipitate was isolated, washed with water and dried. There was thus obtained 6-hydroxy-7-methoxy-3,4-dihydroquinazolin-4-one (11.5 g).

After repetition of the previous reaction, a mixture of 6-hydroxy-7-methoxy-3,4-dihydroquinazolin-4-one (14.18 g), acetic anhydride (110 ml) and pyridine (14 ml) was stirred and heated to 100°C for 2 hours. The mixture was poured onto a mixture (200 ml) of ice and water. The precipitate was isolated, washed with water and dried. There was thus obtained 6-acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one (13 g, 75%).

NMR Spectrum: 2.3 (s, 3H), 3.8 (s, 3H), 7.3 (s, 1H), 7.8 (s, 1H), 8.1 (s, 1H), 12.2 (broad s, 1H).

After repetition of the previous steps, a mixture of 6-acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one (15 g), thionyl chloride (215 ml) and DMF (4.3 ml) was stirred and heated to 90°C for 4 hours. The mixture was cooled to ambient temperature and the thionyl chloride was evaporated. There was thus obtained 6-acetoxy-4-chloro-7-methoxyquinazoline, hydrochloride salt, which was used without further purification.

A mixture of the material so obtained, 3-chloro-4-fluoroaniline (9.33 g) and isopropanol (420 ml) was stirred and heated to 90°C for 5 hours. The mixture was cooled to ambient temperature and the precipitate was isolated, washed in turn with isopropanol and methanol and then dried. There was thus obtained 6-acetoxy-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline hydrochloride salt (14 g, 56%);

NMR Spectrum: 2.4 (s, 3H), 4.0 (s, 3H), 7.5 (t, 1H), 7.6 (s, 1H), 7.75 (m, 1H), 8.05 (m, 1H), 8.8 (s, 1H), 8.95 (s, 1H), 11.5 (broad s, 1H).

A concentrated aqueous ammonium hydroxide solution (30% weight/volume, 7.25 ml) was added to a stirred mixture of the material so obtained and methanol (520 ml). The mixture was stirred at ambient temperature for 17 hours and then heated to 100°C for 1.5 hours. The mixture was cooled and the precipitate was isolated and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (10.62 g, 95%), m.p. >270°C (decomposes);

NMR Spectrum: 4.0 (s, 3H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (s, 1H), 7.85 (m, 1H), 8.2 (m, 1H), 8.5 (s, 1H), 9.45 (s, 1H), 9.65 (s, 1H).

Example 2

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.14 g), 2-(pyrrolidin-1-yl)ethyl chloride hydrochloride (0.607 g), potassium carbonate (3 g) and DMF (28.5 ml) was stirred and heated to 90°C for 5 hours. The mixture was cooled to ambient temperature and poured into water. The precipitate was isolated, dried and purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The material so obtained was recrystallised from ethanol. There was thus obtained

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4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-pyrrolidin-1-ylethoxy)quinazoline (0.813 g, 55%), m.p. 187-188°C;

NMR Spectrum: 1.7 (m, 4H), 2.6 (m, 4H), 2.9 (t, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);

Elemental Analysis: Found C, 60.1; H, 5.4; N, 13.4;

$C_{21}H_{22}ClFN_4O_2$ requires C, 60.5; H, 5.3; N, 13.4%.

Example 3

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.62 g), 2-morpholinoethyl chloride hydrochloride (0.95 g), potassium carbonate (3.6 g) and DMF (40 ml) was stirred and heated to 90°C for 1.5 hours. The mixture was cooled to ambient temperature and poured into water. The precipitate was isolated, dried and purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The material so obtained was recrystallised from isopropanol. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-morpholinoethoxy)quinazoline (1.2 g, 55%), m.p. 229-230°C;

NMR Spectrum: 2.6 (m, 4H), 2.85 (t, 2H), 3.6 (m, 4H), 3.9 (s, 3H), 4.3 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);

Elemental Analysis: Found C, 57.5; H, 4.9; N, 12.7;

$C_{21}H_{22}ClFN_4O_3.0.25H_2O$ requires C, 57.6; H, 5.1; N, 12.8%.

Example 4

A mixture of 1-methylpiperazine (43 ml), 6-(2-bromoethoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline (1.6 g) and ethanol (48 ml) was stirred and heated to reflux for 20 hours. The mixture was evaporated and the residue was purified by column chromatography using a 4:1 mixture of methylene chloride and methanol as eluent. The material so obtained was dissolved in a mixture of methylene chloride and methanol and a saturated aqueous sodium bicarbonate solution was added. The mixture was stirred and heated to reflux. The mixture was cooled to ambient temperature and the precipitate was isolated and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline (0.956 g, 58%), m.p. 88-92°C.

NMR Spectrum: 2.15 (s, 3H), 2.3 (broad m, 4H), 2.5 (broad m, 4H), 2.8 (t, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 57.3; H, 5.6; N, 15.1;
$C_{22}H_{25}ClFN_5O_2$ $0.75H_2O$ requires C, 57.5; H, 5.8; N, 15.2%.

The 6-(2-bromoethoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline used as a starting material was obtained as follows:-

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (10 g), 1,2-dibromoethane (27 ml), potassium carbonate (20 g) and DMF (1 litre) was stirred and heated to 85°C for 2.5 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using ethyl acetate as eluent. There was thus obtained 6-(2-bromoethoxy)-4-(3'-chloro- 4'-fluoroanilino)-7-methoxyquinazoline (10.26 g, 77%), m.p. 232°C (decomposes):
NMR Spectrum: 3.9 (m, 2H), 3.95 (s, 3H), 4.5 (m, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.75 (m, 1H), 7.85 (s, 1H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 48.0; H, 3.3; N, 9.8;
$C_{17}H_{14}BrClFN_3O_2$ requires C, 47.9; H, 3.3; N, 9.8%.

Example 5

A mixture of di-(2-methoxyethyl)amine (1.66 ml), 6-(2-bromoethoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline (1.6 g) and ethanol (48 ml) was stirred and heated to reflux for 18 hours. A second portion (0.53 ml) of di-(2-methoxyethyl)amine was added and the mixture was heated to reflux for a further 18 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using a 97:3 mixture of methylene chloride and methanol as eluent. The material so obtained was dissolved in isopropanol, water was added and the mixture was stirred for 1 hour. The precipitate was isolated and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-{2-[di-(2-methoxyethyl)amino]ethoxy}quinazoline (0.95 g, 53%), m.p. 73-74°C.

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NMR Spectrum: 2.6 (t, 4H), 3.05 (t, 2H), 3.25 (s, 6H), 3.45 (t, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 56.2; H, 6.2; N, 11.3;
$C_{23}H_{28}ClFN_4O_4$ $0.7H_2O$ requires C, 56.2; H, 6.0; N, 11.4%.

Example 6

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (3 g), 2-dimethylaminoethyl chloride hydrochloride (1.5 g), potassium carbonate (7.5 g) and DMF (60 ml) was stirred and heated to 80°C for 5 hours. The mixture was cooled to ambient temperature and poured into water. The precipitate was isolated and dried. The material so obtained was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether and recrystallised from aqueous ethanol. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(2-dimethylaminoethoxy)-7-methoxyquinazoline (1.7 g, 46%), m.p. 133-135°C;
NMR Spectrum: 2.3 (s, 6H), 2.75 (t, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 7.2 (s, 1H), 7.3 (m, 2H), 7.4 (t, 1H), 8.1 (m, 2H), 8.5 (s, 1H), 9.5 (broad s, 1H);
Elemental Analysis: Found C, 58.2; H, 5.2; N, 14.3;
$C_{19}H_{20}ClFN_4O_2$ requires C, 58.4; H, 5.1; N, 14.3%.

Example 7

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.5 g), 2-diethylaminoethyl chloride hydrochloride (0.82 g), potassium carbonate (3.5 g) and DMF (38 ml) was stirred and heated to 90°C for 2 hours. The mixture was cooled to ambient temperature and poured onto ice (75 ml). The precipitate was isolated, recrystallised from a 2:1 mixture of isopropanol and water and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(2-diethylaminoethoxy)-7-methoxyquinazoline (0.98 g, 50%), m.p. 154-156°C;
NMR Spectrum: 1.0 (t, 6H), 2.6 (m, 4H), 2.9 (t, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

Elemental Analysis: Found C, 60.0; H, 5.7; N, 13.2;
$C_{21}H_{24}ClFN_4O_2$ requires C, 60.2; H, 5.8; N, 13.4%.

Example 8

A mixture of 4-(2',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.36 g), 3-dimethylaminopropyl chloride hydrochloride (0.82 g), potassium carbonate (3 g) and DMF (50 ml) was stirred and heated to 80°C for 4 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of hexane and ethyl acetate. There was thus obtained 4-(2',4'-difluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline (0.56 g, 32%), m.p. 131-134°C;
NMR Spectrum: 1.85-2.05 (m, 2H), 2.35 (s, 6H), 2.42 (t, 2H), 3.95 (s, 3H), 4.16 (t, 2H), 7.13 (m, 1H), 7.16 (s, 1H), 7.35 (m, 1H), 7.55 (m, 1H), 7.75 (s, 1H), 8.3 (s, 1H), 9.5 (broad s, 1H);
Elemental Analysis: Found C, 60.9; H, 5.7; N, 14.1;
$C_{20}H_{22}F_2N_4O_2$ $0.3H_2O$ requires C, 61.0; H, 5.7; N, 14.2%.

The 4-(2',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline used as a starting material was obtained as follows:-

A mixture of 6-acetoxy-4-chloro-7-methoxyquinazoline hydrochloride (5.4 g), 2,4-difluoroaniline (2.5 ml) and isopropanol (100 ml) was stirred and heated to reflux for 2 hours. The precipitate was isolated, washed with acetone and with diethyl ether and dried. There was thus obtained 6-acetoxy-4-(2',4'-difluoroanilino)-7-methoxyquinazoline hydrochloride (3.9 g, 53%), m.p. 207-210°C;
NMR Spectrum: 2.4 (s, 3H), 4.05 (s, 3H), 7.25 (m, 1H), 7.48 (m, 1H), 7.55 (s, 1H), 7.63 (m, 1H), 8.7 (s, 1H), 8.85 (s, 1H), 11.6 (broad s, 1H).

A mixture of a portion (3.7 g) of the material so obtained, a concentrated aqueous ammonium hydroxide solution (30% weight/volume, 2 ml) and methanol (140 ml) was stirred at ambient temperature for 2 hours. The precipitate was isolated and washed with diethyl ether. There was thus obtained 4-(2',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.3 g, 40%);

NMR Spectrum: 3.97 (s, 3H), 7.1 (m, 1H), 7.2 (s, 1H), 7.54 (m, 1H), 7.67 (s, 1H), 8.3 (s, 1H), 9.3 (s, 1H), 9.65 (broad s, 1H).

Example 9

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-(2,3-epoxypropoxy)-7-methoxyquinazoline (2 g), morpholine (0.5 ml) and isopropanol (20 ml) was stirred and heated to reflux for 1 hour. The mixture was cooled to ambient temperature and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The material so obtained was recrystallised from ethyl acetate. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(2-hydroxy-3-morpholinopropoxy)-7-methoxyquinazoline (1.4 g, 57%), m.p. 206-207°C;
NMR Spectrum: 2.5 (broad m, 6H), 3.6 (t, 4H), 3.9 (s, 3H), 4.1 (broad m, 3H), 5.0 (broad m, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 57.0; H, 5.2; N, 11.9;
$C_{22}H_{24}ClFN_4O_4$ requires C, 57.1; H, 5.2; N, 12.1%.

The 4-(3'-chloro-4'-fluoroanilino)-6-(2,3-epoxypropoxy)-7-methoxyquinazoline used as a starting material was obtained as follows:-

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (5 g), 2,3-epoxypropyl bromide (1.6 ml), potassium carbonate (5 g) and DMSO (50 ml) was stirred at ambient temperature for 16 hours. The mixture was poured onto a mixture of ice and water. The precipitate was isolated, washed with water and dried. There was thus obtained the required starting material which was used without further purification and gave the following characterising data:-
m.p. 125-126°C (decomposes);
NMR Spectrum: 2.8 (m, 1H), 2.9 (m, 1H), 3.5 (m, 1H), 4.0 (s, 3H), 4.1 (m, 1H), 4.5 (m, 1H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 1H), 7.85 (s, 1H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

Example 10

A mixture of morpholine (13.75 ml), 6-(3-bromopropoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline (2.94 g) and DMF (67 ml) was stirred at ambient temperature for 30 minutes. The mixture was partitioned between ethyl acetate and water. The organic phase was washed with a saturated aqueous sodium bicarbonate solution and with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The material so obtained was recrystallised from toluene. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (0.78 g, 27%); NMR Spectrum: 2.0 (m, 2H), 2.45 (m, 6H), 3.6 (m, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

The 6-(3-bromopropoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline used as a starting material was obtained as follows:-

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (2 g), 1,3-dibromopropane (6.36 ml), potassium carbonate (4 g) and DMF (200 ml) was stirred at ambient temperature for 1 hour. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography using ethyl acetate as eluent. There was thus obtained 6-(3-bromopropoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline in quantitative yield which was used without further purification: NMR Spectrum: 2.4 (m, 2H), 3.7 (t, 2H), 3.95 (s, 3H), 4.3 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

Example 11

A mixture of morpholine (0.17 ml), 6-(2-bromoethoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline (0.4 g) and ethanol (12 ml) was stirred and heated to reflux for 27 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-morpholinoethoxy)quinazoline (0.14 g, 35%).

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NMR Spectrum: 2.6 (m, 4H), 2.85 (t, 2H), 3.6 (m, 4H), 3.9 (s, 3H), 4.3 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

Example 12

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.1 g), 3-diethylaminopropyl chloride hydrochloride (0.7 g), potassium carbonate (3 g) and DMF (30 ml) was stirred and heated to 80°C for 3 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography using a 4:1 mixture of methylene chloride and methanol as eluent. The material so obtained was triturated under a 5:1 mixture of methanol and water. The solid so obtained was dried. There was thus obtained 4-(3'-chloro-4'- fluoroanilino)-6-(3-diethylaminopropoxy)-7-methoxyquinazoline (1.03 g, 70%):

NMR Spectrum: 0.95 (t, 6H), 1.9 (m, 2H), 2.5 (m, 6H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

Elemental Analysis: Found C, 59.4; H, 6.2; N, 12.5;

$C_{22}H_{26}ClFN_4O_2$ $0.7H_2O$ requires C, 59.4; H, 6.2; N, 12.6%.

Example 13

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.28 g), 3-(pyrrolidin-1-yl)propyl chloride hydrochloride (Chem. Abs., 82, 57736; 1.5 g), potassium carbonate (2.8 g) and DMF (20 ml) was stirred and heated to 80°C for 5 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using a 20:3 mixture of methylene chloride and methanol as eluent. The material so obtained (1.1 g) was triturated under ethyl acetate to give 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-pyrrolidin-1-ylpropoxy)quinazoline (0.094 g). The organic solution was evaporated and the residual solid was recrystallised from acetonitrile. There was thus obtained a second crop (0.85 g) of the same product. The material gave the following characterising data -

m.p. 159-161°C.

NMR Spectrum: 1.95 (m, 4H), 3.3 (m, 6H), 3.95 (s, 3H), 4.3 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.9 (m, 1H), 8.1 (s, 1H), 8.2 (m, 1H), 8.5 (s, 1H), 9.8 (broad s, 1H);
Elemental Analysis: Found C, 61.0; H, 5.7; N, 13.1;
$C_{22}H_{24}ClFN_4O_2$ requires C, 61.3; H, 5.6; N, 13.0%.

Example 14

A mixture of 4-(2',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (2.5 g), 3-morpholinopropyl chloride hydrochloride (1.6 g), potassium carbonate (6 g) and DMF (100 ml) was stirred and heated to 60°C for 1 hour. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(2',4'-difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline (1.05 g, 30%), m.p. 151-153°C;
NMR Spectrum: 2.0 (m, 2H), 2.35-2.67 (m, 6H), 3.58 (t, 2H), 3.94 (s, 3H), 4.16 (t, 2H), 7.13 (m, 1H), 7.16 (s, 1H), 7.33 (m, 1H), 7.54 (m, 1H), 7.78 (s, 1H), 8.1 (s, 1H), 9.4 (broad s, 1H);
Elemental Analysis: Found C, 61.4; H, 5.5; N, 12.8;
$C_{22}H_{24}F_2N_4O_3$ requires C, 61.4; H, 5.6; N, 13.0%.

Example 15

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.24 g), 2-(imidazol-1-yl)ethyl chloride (European Patent Application No. 0421210; 2.51 g), potassium carbonate (1.5 g) and DMF (31 ml) was stirred and heated to 90°C for 4 hours and then stored at ambient temperature for 16 hours. The mixture was poured into a mixture of ice and water. The precipitate was isolated, dried and purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The solid so obtained was triturated under methanol. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(2-imidazol-1-ylethoxy)-7-methoxyquinazoline (0.55 g, 34%), m.p. 239-241°C;
NMR Spectrum: 4.0 (s, 3H), 4.4 (t, 2H), 4.5 (t, 2H), 6.9 (s, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.4 (t, 1H), 7.7 (s, 1H), 7.75 (m, 1H), 7.8 (s, 1H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

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Elemental Analysis: Found C, 57.5; H, 4.3; N, 16.7;
$C_{20}H_{17}ClFN_5O_2$ requires C, 58.0; H, 4.1; N, 16.9%.

Example 16

A mixture of imidazole (0.128 g), 6-(2-bromoethoxy)-4-(3'-chloro-4'-fluoroanilino)-7-methoxyquinazoline (0.4 g) and ethanol (12 ml) was stirred and heated to reflux for 66 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(2-imidazol-1-ylethoxy)-7-methoxyquinazoline (0.13 g, 33%);
NMR Spectrum: 4.0 (s, 3H), 4.4 (t, 2H), 4.5 (t, 2H), 6.9 (s, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.4 (t, 1H), 7.7 (s, 1H), 7.75 (m, 1H), 7.8 (s, 1H), 8.1 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H).

Example 17

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (2 g), 3-dimethylaminopropyl chloride hydrochloride (0.99 g), potassium carbonate (5 g) and DMF (100 ml) was stirred and heated to 90°C for 2 hours. The mixture was cooled to ambient temperature and poured into water. The precipitate was isolated and recrystallised from toluene. The resultant solid was purified by column chromatography using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline (0.97 g);
NMR Spectrum: 1.95 (m, 2H), 2.2 (s, 6H), 2.45 (t, 2H), 3.95 (s, 3H), 4.18 (t, 2H), 7.2 (s, 1H), 7.42 (t, 1H), 7.8 (m, 2H), 8.12 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 59.1; H, 5.3; N, 13.6;
$C_{20}H_{22}ClFN_4O_2$ requires C, 59.3; H, 5.5; N, 13.8%.

Example 18

A mixture of 4-(3',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.8 g), 3-dimethylaminopropyl chloride hydrochloride (0.94 g), potassium carbonate (4.5 g) and DMF (90 ml) was stirred and heated to 90°C for 1 hour. The mixture was cooled to ambient

temperature and poured into water. The resultant precipitate was isolated and purified by column chromatography using a 4:1 mixture of methylene chloride and methanol as eluent. The material so obtained was recrystallised from toluene. There was thus obtained 4-(3',4'-difluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline (0.93 g);
NMR Spectrum: 2.0 (m, 2H), 2.2 (s, 6H), 2.45 (m, 2H), 3.9 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (m, 1H), 7.55 (m, 1H), 7.8 (s, 1H), 8.05 (m, 1H), 8.5 (s, 1H), 9.55 (broad s, 1H);
Elemental Analysis: Found C, 61.6; H, 5.7; N, 14.1;
$C_{20}H_{22}F_2N_4O_2$ requires C, 61.8; H, 5.7; N, 14.4%.

The 4-(3',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline used as a starting material was obtained as follows:-

A mixture of 6-acetoxy-4-chloro-7-methoxyquinazoline hydrochloride [obtained from 6-acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one (6 g) and thionyl chloride (87 ml)], 3,4-difluoroaniline (2.9 ml) and isopropanol (170 ml) was stirred and heated to reflux for 4 hours. The precipitate was isolated, washed with isopropanol and dried. There was thus obtained 6-acetoxy-4-(3',4'-difluoroanilino)-7-methoxyquinazoline hydrochloride (7.5 g);
NMR Spectrum: 2.4 (s, 3H), 4.0 (s, 3H), 7.45-7.6 (m, 3H), 7.95 (m, 1H), 8.8 (s, 1H), 8.95 (s, 1H), 11.5 (broad s, 1H).

A mixture of the material so obtained, a concentrated aqueous ammonium hydroxide solution (30% weight/volume, 3.9 ml) and methanol (280 ml) was stirred at ambient temperature for 20 hours. The precipitate was isolated and washed with methanol. There was thus obtained 4-(3',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (5.5 g);
NMR Spectrum: 4.0 (s, 3H), 7.2 (s, 1H), 7.4 (q, 1H), 7.65 (m, 1H), 7.8 (s, 1H), 8.1 (m, 1H), 8.45 (s, 1H), 9.45 (s, 1H), 9.6 (s, 1H).

Example 19

A mixture of 4-(3',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.2 g), 3-morpholinopropyl chloride (0.72 g), potassium carbonate (2 g) and DMF (30 ml) was stirred and heated to 80°C for 2 hours. A further portion (0.3 g) of 3-morpholinopropyl chloride was added and the mixture was heated to 80°C for a further 2 hours. The mixture was cooled to ambient temperature, filtered and the filtrate was evaporated. The residue was purified by column chromatography using a 4:1 mixture of ethyl acetate and methanol as

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eluent. There was thus obtained 4-(3',4'-difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (0.84 g);

NMR Spectrum: 2.0 (m, 2H), 3.6 (t, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (m, 1H), 7.57 (m, 1H), 7.82 (s, 1H), 8.05 (m, 1H), 8.48 (s, 1H), 9.55 (s, 1H);

Elemental Analysis: Found C, 61.1; H, 5.4; N, 12.8;

$C_{22}H_{24}F_2N_4O_3$ requires C, 61.4; H, 5.6; N, 13.0%.

Example 20

A mixture of 4-(3',4'-difluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.2 g), 3-diethylaminopropyl chloride hydrochloride (0.81 g), potassium carbonate (3.5 g) and DMF (30 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature, filtered and evaporated. The residue was purified by column chromatography using a 4:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 6-(3-diethylaminopropoxy)-4-(3',4'-difluoroanilino)-7-methoxyquinazoline (1.14 g);

NMR Spectrum: 0.8 (t, 6H), 1.8 (m, 2H), 3.78 (s, 3H), 4.0 (t, 2H), 7.1 (s, 1H), 7.3 (m, 1H), 7.45 (m, 1H), 7.65 (s, 1H), 7.9 (m, 1H), 8.34 (s, 1H), 9.4 (broad s, 1H);

Elemental Analysis: Found C, 63.4; H, 6.3; N, 13.6;

$C_{22}H_{26}F_2N_4O_2$ requires C, 63.4; H, 6.3; N, 13.5%.

Example 21

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.2 g), 3-piperidinopropyl chloride hydrochloride (0.82 g), potassium carbonate (3 g) and DMF (30 ml) was stirred and heated to 80°C for 2 hours. The mixture was cooled to ambient temperature, filtered and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The solid so obtained was triturated under diethyl ether. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-piperidinopropoxy)quinazoline (0.94 g);

NMR Spectrum: 1.4-1.7 (m, 6H), 2.0 (m, 2H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8-8.0 (m, 2H), 8.1 (m, 1H), 8.5 (s, 1H), 9.55 (s, 1H);

Elemental Analysis: Found C, 61.8; H, 5.8; N, 12.6;

$C_{23}H_{26}ClFN_4O_2$ requires C, 62.1; H, 5.9; N, 12.6%.

Example 22

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.5 g), 2-piperidinoethyl chloride hydrochloride (0.86 g), potassium carbonate (3 g) and DMF (40 ml) was stirred and heated to 90°C for 1 hour. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The material so obtained was recrystallised from toluene. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-piperidinoethoxy)quinazoline (0.77 g);
NMR Spectrum: 1.3-1.6 (m, 6H), 2.8 (t, 2H), 3.95 (s, 3H), 4.25 (t, 2H), 7.2 (s, 1H), 7.45 (t, 1H), 7.8 (m, 2H), 8.12 (m, 1H), 8.48 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 61.0; H, 5.7; N, 13.0;
$C_{22}H_{24}ClFN_4O_2$ requires C, 61.3; H, 5.6; N, 13.0%.

Example 23

A mixture of 4-(3'-chloro-4'-fluoroanilino)-6-hydroxy-7-methoxyquinazoline (1.5 g), 3-(imidazol-1-yl)propyl chloride (0.67 g), potassium carbonate (3 g) and DMF (40 ml) was stirred and heated to 90°C for 1 hour. A second portion (0.12 g) of the propyl chloride was added and the mixture was heated to 90°C for a further hour. The mixture was cooled to ambient temperature, filtered and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-6-(3-imidazol-1-ylpropoxy)-7-methoxyquinazoline (0.66 g);
NMR Spectrum: 2.5 (m, 2H), 4.12 (s, 3H), 4.25 (t, 2H), 4.35 (t, 2H), 7.08 (s, 1H), 7.4 (d, 2H), 7.6 (t, 1H), 7.8 (s, 1H), 7.95 (m, 2H), 8.25 (m, 1H), 8.65 (s, 1H), 9.7 (broad s, 1H);
Elemental Analysis: Found C, 58.2; H, 4.6; N, 16.6;
$C_{21}H_{19}ClFN_5O_2.0.2H_2O$ requires C, 58.5; H, 4.5; N, 16.2%.

The 3-(imidazol-1-yl)propyl chloride used as a starting material was obtained as follows:-

A solution of imidazole (5.4 g) in DMF (20 ml) was added dropwise to a stirred mixture of sodium hydride (60% dispersion in mineral oil, 3.3 g) which was washed with

petroleum ether (b.p. 40-60°C)] in DMF (10 ml). The resultant solution was added to a solution of 3-bromochloropropane (13 g) in DMF (70 ml) which had been cooled in an ice bath. The mixture was stirred at 0°C for 1 hour. The mixture was poured into a saturated aqueous sodium bicarbonate solution. The resultant mixture was filtered and the filtrate was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained 3-(imidazol-1-yl)propyl chloride (8.3 g); NMR Spectrum: 2.2 (m, 2H), 3.55 (t, 2H), 4.1 (t, 2H), 6.9 (s, 1H), 7.18 (s, 1H), 7.6 (s, 1H).

Example 24

A 1M solution of hydrogen chloride in diethyl ether (65 ml) was added to a solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (30.1 g) in diethyl ether (545 ml) and DMF (250 ml). The mixture was stirred at ambient temperature for 1 hour. The precipitate was isolated, washed with diethyl ether and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline hydrochloride salt (32.1 g), m.p. 251-255°C;
NMR Spectrum: 2.3 (m, 2H), 3.2-3.4 (m, 6H), 3.9 (broad s, 4H), 3.95 (s, 3H), 4.35 (t, 2H), 7.22 (s, 1H), 7.4 (t, 1H), 7.9 (m, 1H), 8.12 (s, 1H), 8.2 (m, 1H), 8.55 (s, 1H), 10.0 (s, 1H);
Elemental Analysis: Found C, 54.5; H, 5.3; N, 11.7;
$C_{22}H_{24}ClFN_4O_3.1HCl.0.08H_2O$ requires C, 54.5; H, 5.2; N, 11.6%.

Example 25

A 1M solution of hydrogen chloride in diethyl ether (15 ml) was added to a solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (2.2 g) in DMF (20 ml) and the mixture was stirred at ambient temperature for 2 hours. The precipitate was isolated, washed with diethyl ether and dried under vacuum at 80°C. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline dihydrochloride salt (2.3 g);
NMR Spectrum: 2.3 (m, 2H), 3.2-3.6 (m, 6H), 4.0 (m, 7H), 4.35 (t, 2H), 7.4 (s, 1H), 7.55 (t, 1H), 7.8 (m, 1H), 8.15 (m, 1H), 8.6 (s, 1H), 8.9 (s, 1H).

Elemental Analysis: Found C, 50.7; H, 5.0; N, 10.5; Cl, 13.1;
$C_{22}H_{24}ClFN_4O_3$ 2HCl requires C, 50.8; H, 5.0; N, 10.8; Cl, 13.6%.

Example 26

A solution of L-(2R,3R)-(+)-tartaric acid (1.03 g) in THF (50 ml) was added to a solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (1.53 g) in THF (100 ml) and the mixture was stirred at ambient temperature for 2 hours. The mixture was filtered, washed with THF and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline di-L-tartaric acid salt (2 g), m.p. 136-140°C (phase change at 111°C);
NMR Spectrum: 2.2 (m, 2H), 2.5-2.6 (m, 6H), 3.6 (t, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 4.3 (s, 4H), 7.2 (s, 1H), 7.45 (t, 1H), 7.8 (m, 2H), 8.15 (m, 1H), 8.5 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 48.8; H, 5.2; N, 7.6;
$C_{22}H_{24}ClFN_4O_3$ 2 tartaric acid requires C, 48.4; H, 4.6; N, 7.5%.

Example 27

A solution of fumaric acid (0.8 g) in a mixture of methylene chloride and DMF was added to a solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline (1.5 g) in a mixture of methylene chloride (50 ml) and sufficient DMF to complete the dissolution. The mixture was stirred at ambient temperature for 2 hours. The precipitate was isolated, washed with methylene chloride and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline difumaric acid salt (2.12 g), m.p. 199-201°C;
NMR Spectrum: 2.0 (m, 2H), 2.5-2.7 (m, 6H), 3.6 (t, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 6.6 (s, 2H), 7.2 (s, 1H), 7.42 (t, 1H), 7.8 (m, 2H), 8.2 (m, 1H), 8.48 (s, 1H), 9.5 (s, 1H);
Elemental Analysis: Found C, 51.8; H, 4.7; N, 8.3;
$C_{22}H_{24}ClFN_4O_3$ $1H_2O$ 2 fumaric acid requires C, 51.5; H, 5.2; N, 8.0%.

Example 28

A solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline (1.4 g) in the minimum volume of THF was added to a solution of citric acid

(1.5 g) in THF (30 ml). The resultant mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated and triturated under acetone. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline containing 1.8 equivalents of citric acid (1.3 g), m.p. 160-163°C;

NMR Spectrum: 2.1 (m, 2H), 2.6-2.8 (m, 8H), 3.65 (t, 4H), 3.95 (s, 3H), 4.2 (t, 2H), 7.2 (s, 1H), 7.4 (t, 1H), 7.8 (m, 2H), 8.2 (m, 1H), 8.48 (s, 1H), 9.6 (s, 1H);

Elemental Analysis: Found C, 50.0; H, 5.2; N, 7.2;

$C_{22}H_{24}ClFN_4O_3$ 1.8 citric acid requires C, 49.7; H, 4.9; N, 7.1%.

Example 29

A solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline (5 g) in THF (250 ml) was added to a stirred solution of methanesulphonic acid (2.4 g) in THF (100 ml). The resultant mixture was stirred at ambient temperature for 1 hour. The precipitate was isolated, slurried in acetone and re-isolated. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline di-methanesulphonic acid salt (6.5 g), m.p. 242-245°C;

NMR Spectrum: 2.3 (m, 2H), 2.45 (s, 6H), 3.0-3.8 (m, 10H), 4.1 (s, 3H), 4.35 (t, 2H), 7.4 (s, 1H), 7.55 (t, 1H), 7.75 (m, 1H), 8.0 (m, 1H), 8.15 (s, 1H), 8.9 (s, 1H), 9.6 (s, 1H), 11.0 (s, 1H);

Elemental Analysis: Found C, 44.1; H, 5.2; N, 8.6;

$C_{22}H_{24}ClFN_4O_3$ 1.13H_2O 2CH_3SO_3H requires C, 43.7; H, 5.2; N, 8.5%.

Example 30

A solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline (1.5 g) in a mixture of DMA (10 ml) and methylene chloride (50 ml) was added to a mixture of concentrated sulphuric acid (1.5 ml) and methylene chloride (20 ml). The resultant mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated, washed with acetone and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline di-sulphuric acid salt (2.7 g), m.p. >250°C;

NMR Spectrum: 2.3 (m, 2H), 3.0-3.8 (m, 10H), 4.02 (s, 3H), 4.35 (t, 2H), 7.38 (s, 1H), 7.53 (t, 1H), 7.77 (m, 1H), 8.05 (m, 1H), 8.15 (s, 1H), 8.92 (s, 1H);

Elemental Analysis: Found C, 39.0; H, 4.2; N, 8.2;

$C_{22}H_{24}ClFN_4O_3$ $2H_2O$ $2H_2SO_4$ requires C, 38.9; H, 4.75; N, 8.3%.

Example 31

A solution of 4-toluenesulphonic acid monohydrate (1.12 g) in THF (20 ml) was added to a solution of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline (1.3 g) in THF (60 ml). The resultant mixture was stirred at ambient temperature for 4 hours. The precipitate was isolated, washed in turn with THF and acetone and dried. There was thus obtained 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline di-4-toluenesulphonic acid salt (1.54 g), m.p. 169-173°C;

NMR Spectrum: 2.3 (m, 8H), 3.0-3.8 (m, 10H), 4.0 (s, 3H), 4.3 (t, 2H), 7.1 (d, 4H), 7.34 (s, 1H), 7.5 (d, 4H), 7.54 (t, 1H), 7.7 (m, 1H), 7.95 (m, 1H), 8.1 (s, 1H), 8.9 (s, 1H), 11.0 (broad s, 1H);

Elemental Analysis: Found C, 52.8; H, 4.9; N, 6.8;

$C_{22}H_{24}ClFN_4O_3$ $1.5H_2O$ $2CH_3C_6H_4SO_3H$ requires C, 52.8; H, 5.3; N, 6.85%.

Example 32

The following illustrate representative pharmaceutical dosage forms containing the compound of formula I, or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

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(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur.	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone	2.25
	Magnesium stearate	3.0

(c)	Tablet III	mg/tablet
	Compound X	1.0
	Lactose Ph.Eur	93.25
	Croscarmellose sodium	4.0
	Maize starch paste (5% w/v paste)	0.75
	Magnesium stearate	1.0

(d)	Capsule	mg/capsule
	Compound X	10
	Lactose Ph. Eur.	488.5
	Magnesium stearate	1.5

(e)	Injection I	(50 mg/ml)
	Compound X	5.0% w/v
	1M Sodium hydroxide solution	15.0% w/v
	0.1M Hydrochloric acid (to adjust pH to 7.6)	
	Polyethylene glycol 400	4.5% w/v
	Water for injection to 100%	

(f)	Injection II	(10 mg/ml)
	Compound X	1.0% w/v
	Sodium phosphate BP	3.6% w/v
	0.1M Sodium hydroxide solution	15.0% v/v
	Water for injection to 100%	

(g)	Injection III	(1mg/ml,buffered to pH6)
	Compound X	0.1% w/v
	Sodium phosphate BP	2.26% w/v
	Citric acid	0.38% w/v
	Polyethylene glycol 400	3.5% w/v
	Water for injection to 100%	

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

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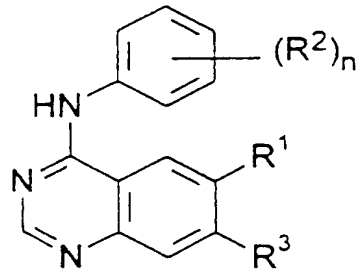
CLAIMS

1. A quinazoline derivative of the formula I



I

wherein n is 1, 2 or 3 and each R^2 is independently halogeno, trifluoromethyl or (1-4C)alkyl;
R^3 is (1-4C)alkoxy; and
R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy, di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(2-4C)alkoxy, thiamorpholino-(2-4C)alkoxy, 1-oxothiamorpholino-(2-4C)alkoxy or 1,1-dioxothiamorpholino-(2-4C)alkoxy, and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent;
or a pharmaceutically-acceptable salt thereof.

2. A quinazoline derivative of the formula I as claimed in claim 1 wherein n is 1, 2 or 3 and each R^2 is independently halogeno, trifluoromethyl or (1-4C)alkyl;
R^3 is (1-4C)alkoxy; and
R^1 is di-[(1-4C)alkyl]amino-(2-4C)alkoxy, pyrrolidin-1-yl-(2-4C)alkoxy, piperidino-(2-4C)alkoxy, morpholino-(2-4C)alkoxy, piperazin-1-yl-(2-4C)alkoxy, 4-(1-4C)alkylpiperazin-1-yl-(2-4C)alkoxy, imidazol-1-yl-(2-4C)alkoxy or di-[(1-4C)alkoxy-(2-4C)alkyl]amino-(2-4C)alkoxy, and wherein any of the above-mentioned R^1 substituents comprising a CH_2 (methylene) group which is not attached to a N or O atom optionally bears on said CH_2 group a hydroxy substituent.

or a pharmaceutically-acceptable salt thereof.

3. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;

R^3 is methoxy; and

R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, 2-[di-(2-methoxyethyl)amino]ethoxy or 3-morpholino-2-hydroxypropoxy;

or a pharmaceutically-acceptable mono- or di-acid-addition salt thereof.

4. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3'-chloro, 3'-bromo, 3'-methyl, 2',4'-difluoro, 2',4'-dichloro, 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;

R^3 is methoxy; and

R^1 is 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(imidazol-1-yl)ethoxy, 2-[di-(2-methoxyethyl)amino]ethoxy or 3-morpholino-2-hydroxypropoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

5. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3'-chloro, 3'-bromo, 3'-methyl, 2',4'-difluoro, 2',4'-dichloro, 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;

R^3 is methoxy; and

R^1 is 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 3-(pyrrolidin-1-yl)propoxy, 3-morpholinopropoxy or 3-morpholino-2-hydroxypropoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

6. A quinazoline derivative of the formula I as claimed in claim 1 wherein $(R^2)_n$ is 3',4'-difluoro, 3',4'-dichloro, 3'-fluoro-4'-chloro or 3'-chloro-4'-fluoro;

R^3 is methoxy; and

R^1 is 3-morpholinopropoxy.

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or a pharmaceutically-acceptable acid-addition salt thereof.

7. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-pyrrolidin-1-ylethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

8. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(2-morpholinoethoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

9. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3'-chloro-4'-fluoroanilino)-6-(3-diethylaminopropoxy)-7-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

10. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-pyrrolidin-1-ylpropoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

11. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3'-chloro-4'-fluoroanilino)-6-(3-dimethylaminopropoxy)-7-methoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

12. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3',4'-difluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

13. The quinazoline derivative of the formula I as claimed in claim 1 being:-

4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-piperidinopropoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

14. The quinazoline derivative of the formula I as claimed in claim 1 being:-

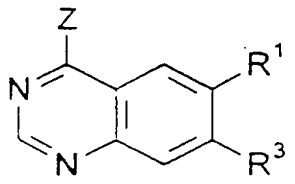
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

15. The hydrochloride salt of the quinazoline derivative of the formula I as claimed in claim 14.

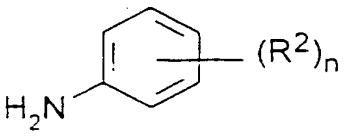
16. A process for the preparation of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15 which comprises:-

(a) the reaction of a quinazoline of the formula II



II

wherein Z is a displaceable group, with an aniline of the formula III



III

(b) for the production of those compounds of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, the alkylation of a quinazoline derivative of the formula I wherein R^1 is a hydroxy group;

(c) for the production of those compounds of the formula I wherein R^1 is an amino-substituted (2-4C)alkoxy group, the reaction of a compound of the formula I wherein R^1 is a hydroxy-(2-4C)alkoxy group, or a reactive derivative thereof, with an appropriate amine; or

(d) for the production of those compounds of the formula I wherein R^1 is a hydroxy-amino-(2-4C)alkoxy group, the reaction of a compound of the formula I wherein R^1 is a 2,3-epoxypropoxy or 3,4-epoxybutoxy group with an appropriate amine.

and when a pharmaceutically-acceptable salt of a quinazoline derivative of the formula I is required it may be obtained by reaction of said compound with a suitable acid using a conventional procedure.

17. A pharmaceutical composition which comprises a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15 in association with a pharmaceutically-acceptable diluent or carrier.

18. The use of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15 in the

BNSDOCID: <WO 9633980A1 I >

manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal.

19. A method for producing an anti-proliferative effect in a warm-blooded animal in need of such treatment which comprises administering to said animal an effective amount of a quinazoline derivative of the formula I, or a pharmaceutically-acceptable salt thereof, as claimed in any one of claims 1 to 15.

INTERNATIONAL SEARCH REPORT

Inter ...nal Application No
PCT/GB 96/00961

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/94 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 566 226 (ZENECA) 20 October 1993 cited in the application see claims	1,2, 16-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search
19 June 1996

Date of mailing of the international search report
25.06.96

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer
Francois, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 96/00961

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		CA-A-	2086968	21-07-93
		DE-D-	69300754	14-12-95
		DE-T-	69300754	28-03-96
		ES-T-	2078798	16-12-95
		NZ-A-	245662	26-09-95
		SK-A-	1693	09-09-93
		US-A-	5457105	10-10-95
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